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THE ACTION OF 5-HYDROXYTRYPTAMINE ON THE BLOOD VESSELS OF THE HUMAN HAND AND FOREARM

BY

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Rapport, Green, and Page in 1948 isolated a vasoactive substance ("serotonin") from beef serum and this was later shown (Rapport, 1949) to be 5-hydroxytryptamine, the creatinine sulphate (5-HT) of which has since been produced synthetically (Hamlin and Fischer, 1951; Specter, Heinzelmann, and Weisblat, 1951). The presence of 5-HT has been demonstrated in many body tissues and fluids of man and animals, including the alimentary canal (Dalgliesh, Toh, and Work, 1953), brain and urine (Twarog and Page, 1953), enterochromaffin tissue (Erspamer and Asero, 1952), blood serum (Erspamer and Sala, 1954) and platelets (Zucker and Borelli, 1955). It has been suggested that this substance plays a part in haemostasis (Zucker, 1947), in kidney function (Erspamer and Sala, 1954) and in central nervous activity (Stole, 1947). Its effects on the circulation suggest that it has a role in the regulation of vascular tone (Page, 1952). The mechanism of this last effect is still obscure and the present paper attempts to define the actions of 5-HT on peripheral blood vessels in man by observation of blood flow, heat loss and volume changes in the upper limb during local arterial injections.

METHODS

Experiments were carried out on 8 healthy subjects (7 men and 1 woman) of ages 18–32 years. The subject lay recumbent on a couch for half to three-quarters of an hour before the beginning of the experiment. The room temperature was 20–24° C. in different experiments and did not vary by more than 1° C. in any one experiment. An infusion of 0.9% saline was started at a rate of 4 ml./min. through a needle inserted into the left brachial artery at the elbow and connected by a short length of polythene tubing to one of two mechanically driven syringes. These syringes could be driven simultaneously and the infusion changed from saline to drug solution without delay.

For each experiment 2–5 mg. of 5-hydroxytryptamine creatinine sulphate salt (Abbott) was dissolved in 5 ml. of saline in a sealed glass ampoule and boiled for 15–20 min. This solution was then diluted so that the dose for 1 min. was contained in 4 ml. of saline. This treatment has been shown not to affect the potency of 5-HT as determined by its action on the guinea-pig ileum (Mongar, personal communication). Infusions were given into the brachial artery of one side in doses ranging from 0.25 to 16 μg./min. for periods of 5–15 min. All doses are expressed as weight of the creatinine sulphate salt.

Observations were made on both limbs simultaneously, the right being used as a control throughout. Measurements of blood flow through the forearms or hands were made by venous occlusion plethysmography at 35 and 32° C. respectively using the temperature-controlled, stirred plethysmographs described by Greenfield (1954). Volume changes in the hands and forearms were also measured with the plethysmographs. In some experiments heat elimination from the pulps of the middle fingers of the two sides was measured with copper-tellurium heat-flow discs (Hatfield, 1950) simultaneously with measurements of blood flow or volume change.

RESULTS

Subjective Effects

Soon after beginning the infusion of 5-HT in doses of 1 μg./min. and above, a sensation of tingling was felt in the hand and lower forearm which decreased somewhat throughout the infusion period and subsided within a few minutes of the end of the infusion. No generalized effects were noted.

Hand Circulation

In three subjects the hand blood flow was measured plethysmographically during infusions of 0.25 to 16 μg./min. (Fig. 1). Doses of 1 μg./min. or less had no effect on the flow; doses of 4 and 16 μg./min. reduced the flow, 16 μg. appearing to arrest the circulation almost completely. During the infusion of the drug the hand volume increased and when the wrist cuff was inflated to impede the venous return the additional amount of blood which could be accommodated in the hand was less than before the infusion, and hence the inter-

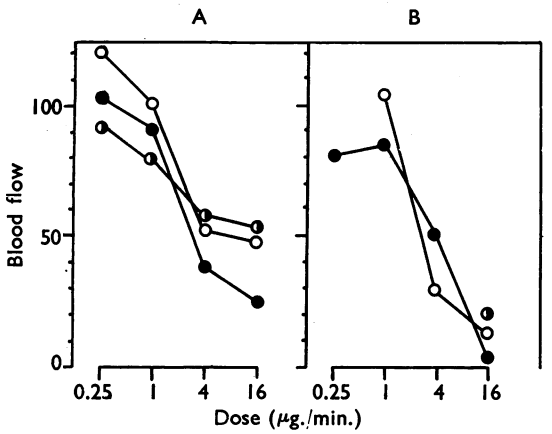


FIG. 1.—Dose-response curves for 5-hydroxytryptamine on forearm (A) and on hand (B) blood flow. The flow (ordinates) is expressed as a percentage of the predicted value if no infusion had been given, determined from the ratios of the resting levels of flow in the control and experimental sides. (See Greenfield and Patterson, 1954.)

pretation of the inflow curves was rendered somewhat uncertain. Typical examples of hand blood-flow records before and during 5-HT infusion are shown in Fig. 2.

In one of the above experiments the heat flow was recorded from the pulps of the middle fingers simultaneously with the blood flow measurements and the changes in heat elimination confirmed the interpretation of the plethysmograph findings (Fig. 3). The reduction in hand circulation during 5-HT infusions was seen in 2 further experiments in which the heat elimination was recorded simultaneously with changes in volume of the hands (Figs. 4 and 5A). Concurrent with the fall in heat elimination the hand volume increased.

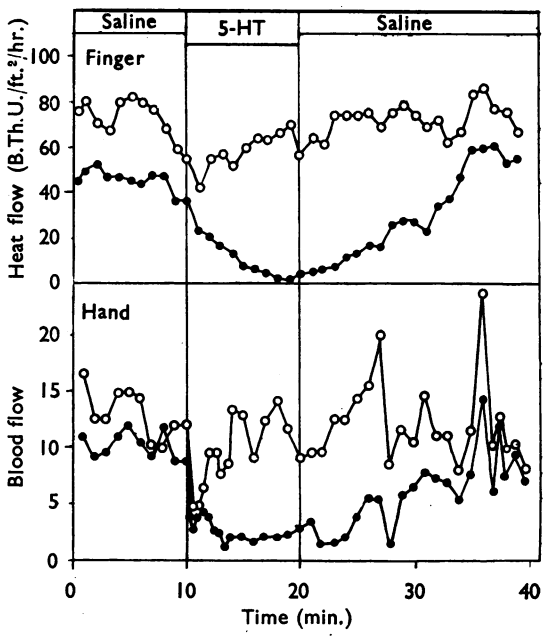


FIG. 3.—Simultaneous hand blood flow and finger heat flow measurements before, during, and after infusion of 16 μg./min. 5-hydroxytryptamine into the brachial artery of the left side. ● Left (injected) side; ○ right (control) side. Blood flow in ml./100 ml./min.

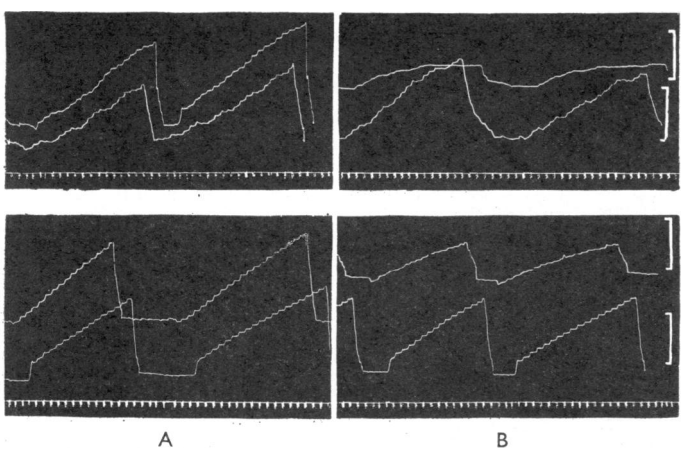


FIG. 2.—Typical plethysmographic records of hand blood flow (upper frames) and forearm blood flow (lower frames). A, 1 min. before, and B, 8 min. after the beginning of infusions of 5-hydroxytryptamine (4 μg./min.). The upper record in each frame was obtained from the experimental limb and the lower record from the opposite (control) limb. The calibration marks represent 5 ml. increases in volume. Time, 1 sec.

In Fig. 6 the rate of fall in heat elimination from the finger pulp in 3 subjects following the onset of infusions of 5-HT at 16 μg./min. is plotted logarithmically against time and compared with the rate of fall in a subject in whom the circulation to the arm was arrested by inflation of a pneumatic cuff around the upper arm to 260 mm. Hg. The results demonstrate that the infusion arrested the circulation through the fingers completely or almost completely.

With doses of 16 μg./min. there was an initial transient vasoconstriction in the control hand (Figs. 3 and 4). No such effect was seen in the control forearm (Figs. 5B and 7), and since the constriction was transient and coincided with the onset of the sensation of tingling it was probably reflex

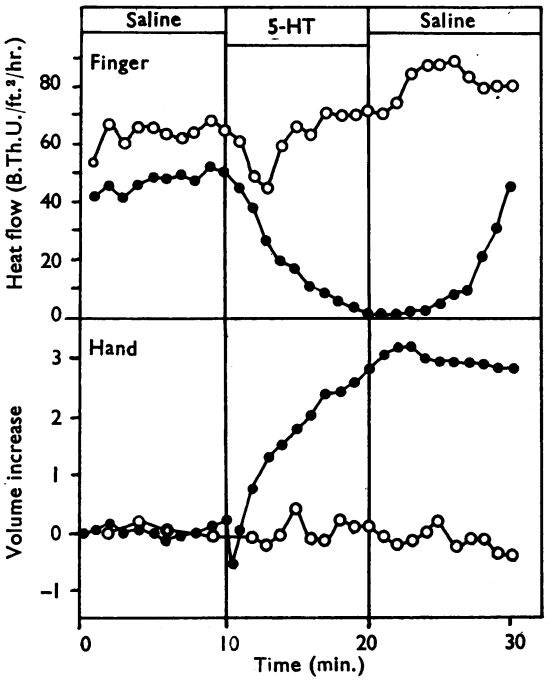


FIG. 4

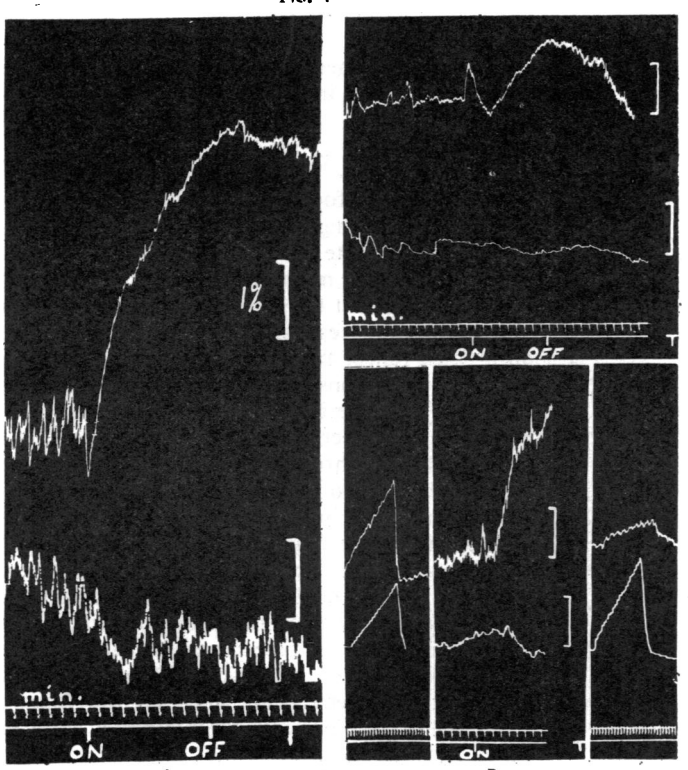
in origin and not due to the arrival of 5-HT in the control limb.

Observations of colour changes in the hands and fingers were made in 2 subjects during infusion of 5-HT. A bright red flush of the skin of the hand

FIG. 4.—Simultaneous finger heat flow and hand volume change during infusion of 16 μg./min. of 5-hydroxytryptamine into the left brachial artery. ● Left (injected) side; ○ right (control) side. Volume changes are expressed as percentage increase from the resting volume (465 ml.).

FIG. 5.—Records of volume changes during infusions of 5-hydroxytryptamine into the left brachial artery. A, *Hand*, during infusion of 16 μg./min. B, *Forearm*. *Upper record*, during infusion of 1 μg./min. *Lower record*, left-hand frame, inflow curves before infusion; centre frame, forearm volume change during infusion of 16 μg./min.; and right-hand frame, inflow curves 8 min. after the start of the infusion. The calibration marks represent a change in volume of 1% and also indicate the static calibration. The lower tracing in each record is from the control limb.

FIG. 6.—Comparison of the rate of fall in heat elimination (log scale) from a finger of each of 3 subjects immediately following the start, at time 0, of an infusion of 16 μg./min. 5-hydroxytryptamine into the brachial artery (circles) and the rate of fall following arrest, at time 0, of the circulation by a pneumatic cuff around the upper arm inflated to 260 mm. Hg (dots).



A FIG. 5 B

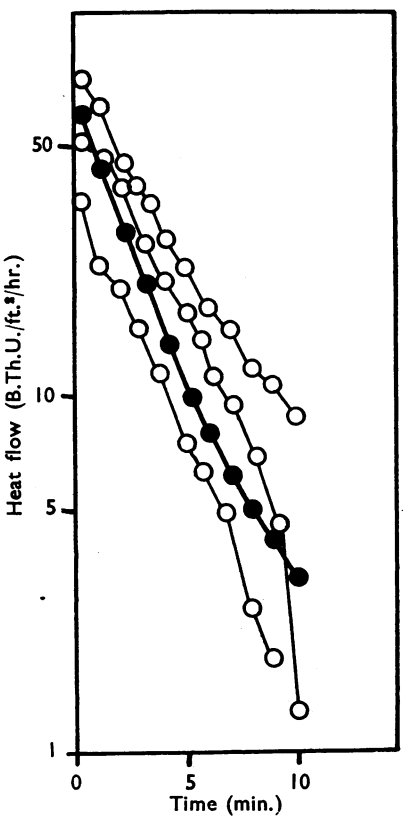


FIG. 6

and fingers appeared within 1–2 min. and was followed after about 5–7 min. by a dusky blue discoloration of the fingers which increased during the remainder of the 10 min. infusion so that by the end of this period the fingers were deeply cyanotic. This appearance subsided during the subsequent 10 min., the hand and fingers returning to their normal colour.

Forearm Circulation

Fig. 5B illustrates the increases in forearm volume which occurred during infusion of 1 and 16 μg./min. of 5-HT into the brachial artery. With 16 μg. the increase was of the order 2–3%. In Figs. 2 and 5B (lower frame) are shown records obtained by venous occlusion plethysmography before and during infusions of 4 and 16 μg./min. at a time when the changes in volume were maximal. If it is valid in view of the increase in forearm volume to assess changes in the rate of arterial inflow from these records at least qualitatively, then it is clear that the drug causes a reduction in forearm flow.

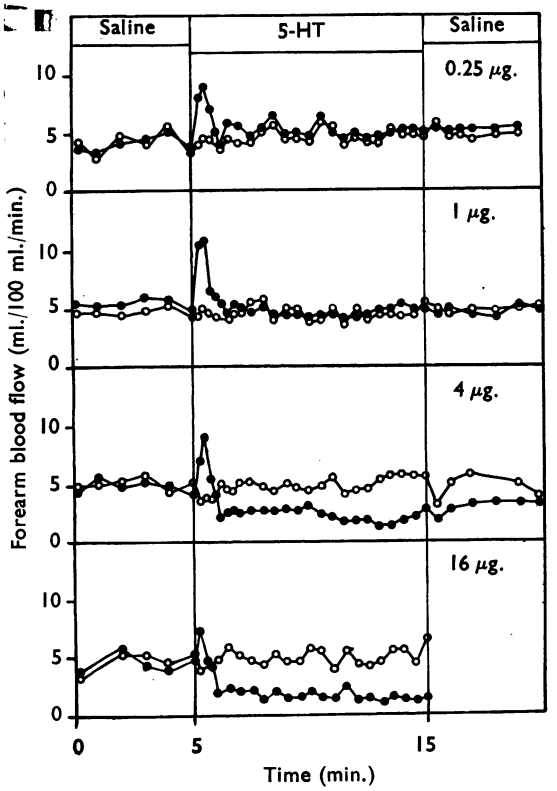


FIG. 7.—The response of the forearm blood flow in one subject to four doses of 5-hydroxytryptamine (indicated at right of each frame) infused into the brachial artery of the left side. ● Left forearm; ○ right forearm.

Fig. 7 illustrates the effects of various doses on the forearm blood flow on the assumption that the plethysmographic records are indicative of the true rates of arterial inflow. At all dose levels the forearm flow was briefly increased during the first 60–90 sec. of the infusion. At dose levels of 1 μg./min. or less the flow during the remainder of the infusion did not differ from that of the control side. At 4 and 16 μg./min., following the initial transient increase, the forearm flow fell to half to one-third of the resting value and remained so for the rest of the infusion. Fig. 1 shows the dose-response curve for the forearm flow during the last half of the infusion period in 3 subjects.

The colour changes in the forearm were as striking as those in the hand. Infusion of doses of 4 μg. or more caused a diffuse flush of the forearm skin, particularly on the flexor surface; this persisted throughout the infusion and gradually subsided afterwards. At no time was the skin of the forearm cyanosed.

In one subject, who received an intra-arterial infusion at a rate of 4 μg./min. for 8 min., and in 3 who received 16 μg./min. for 10–15 min., there developed, after a latent period of some hours, small petechial haemorrhages either scattered diffusely over the flexor surface of the forearm or grouped on the flexor surface of the wrist and lower forearm. These were associated with a slight itching and faded in 24–48 hr.

DISCUSSION

The increase in forearm and hand volume during 5-HT infusions might render invalid the assessment of the rate of arterial inflow by the plethysmographic method, especially as it seems most probable that the increase is due to dilatation of the capacity vessels. That the inflow curves do at least reflect the direction of change of flow, however, is demonstrated by the fact that, in the hand, the decrease in slope of the curves is closely paralleled by a decrease in heat elimination. That the blood flow through the skin of the hand is very much reduced in spite of dilated capillaries is further indicated by the development of cyanosis of the skin of the fingers during the infusion. In the forearm the apparent reduction in flow obtained by the plethysmographic method could not be checked by calorimetric or skin temperature measurements, since these cannot be used to assess changes in forearm circulation with any degree of accuracy. The effect of 5-HT on the forearm flow could, therefore, not be interpreted with the same certainty as in the hand.

The increase in forearm and hand volume during infusion of the drug must be contributed to—at least in part—by the dilatation of the minute vessels of the skin. It is possible that other factors such as venoconstriction (Reid, 1952) or oedema formation may contribute, but the present experiments provide no evidence on these points. The development of petechial haemorrhages following the larger doses in some subjects is indicative of capillary damage. Whether some of the effects of 5-HT on the peripheral vessels might be accounted for by release of histamine is still uncertain. Feldberg and Smith (1953) have shown that large doses of 5-HT cause release of histamine from the perfused skin flap of the cat, accompanied by vasoconstriction and oedema formation. Although histamine, in a wide range of doses, injected intra-arterially into the forearm or hand in man, always causes dilatation of the resistance vessels and an increase in flow (Duff, Greenfield, Shepherd, and Thompson, 1953), it is conceivable that the direct constrictor action of 5-HT on the resistance vessels might counteract the dilator action of histamine on these vessels while leaving unopposed its action on the capillaries. On the other hand, Reid (1952) demonstrated that the flush of the skin caused by intradermal injection of 5-HT was not accompanied by itching or a weal, and preliminary experiments in this department indicate that there is no diminution of the flush following intra-arterial injection of antihistamine.

The effect of intra-arterial administration of 5-HT in doses of more than 1 μg./min. on the circulation in the hand and forearm in man is essentially the same. The blood flow is very considerably reduced, while there is an increase in the volume of the part and a flushing of the skin. In the forearm a transient vasodilatation precedes the vasoconstriction and with doses of less than 1 μg./min. the transient dilatation alone is observed. This dilatation did not increase with increasing doses.

These results demonstrate that intra-arterial 5-HT constricts those vessels which control the rate of blood flow (the arterioles) and at the same time dilates the minute vessels of the skin.

In recent years a clinical and pathological triad has been described (Thorson, Biörck, Björkman, and Waldenström, 1954; Isler and Hedinger, 1953; Rosenbaum, Santer, and Claudon, 1953; and Branwood and Bain, 1954) consisting of carcinoid tumour, pulmonary stenosis and a reddish-blue colour of the skin often associated with periodic attacks of intense flushing. Pernow and Waldenström (1954) have demonstrated an increase in substances resembling 5-HT in the blood and urine of 2 patients with carcinoid tumours during attacks of flushing. They have suggested that the vasomotor symptoms are caused by a discharge of 5-HT. The skin colour changes observed in the present experiments are consistent with this view.

Summary

1. The circulation in the upper limb has been observed during infusions of 5-hydroxytryptamine creatinine sulphate (5-HT) in doses of 0.25 to 16 μg./min. into the human brachial artery.

2. With doses of more than 1 μg./min. the forearm and hand blood flow decreases, the volume increases and there is a marked flushing of the skin.

3. 5-HT causes a constriction of the vessels mainly responsible for resistance to flow, and a dilatation of the vessels responsible for the colour of the skin.

4. In the forearm the fall in flow is preceded by a transient vasodilatation.

5. As the infusion continues, cyanosis gradually develops in the skin of the fingers but not elsewhere.

6. In some subjects small petechial haemorrhages were observed some hours after the infusion.

7. The colour changes in the skin are similar to those that have been described in some cases of carcinoid tumour of the intestine.

We wish to express our thanks to those students and colleagues who acted as subjects, to Professor A. D. M. Greenfield for advice and criticism in the preparation of the paper, and to Abbott Laboratories, Chicago, for a supply of 5-hydroxytryptamine.

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